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RESEARCH ARTICLE

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Sweet syndrome induced by SARS-CoV-2 vaccines: A systematic review of patient-report studies

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ABSTRACT

Since COVID-19 became a global pandemic in 2020, the development and application of SARS-CoV-2 vaccines has become an important task to prevent the spread of the epidemic. In addition to the safety and efficacy of COVID-19 vaccines, the adverse reactions caused by vaccines in a small number of people also deserve our attention. We aimed to discuss and analyze the possible causes of Sweet syndrome caused by the COVID-19 vaccine by integrating the effective information from 16 patients and combining it with the latest views on the innate immune mechanism. We searched the PubMed and Embase databases for published patient reports on the occurrence or recurrence of Sweet syndrome after COVID-19 vaccination. We summarized the basic information of the patients, the type of vaccination, the presence of underlying diseases, and the clinical manifestations, clinical treatment and prognosis of the patients. The results were reported in narrative methods and were sorted into tables. We initially identified 53 studies. 16 articles were included through full-text screening. Based on the table we compiled, we generally concluded that the first dose of any type of COVID-19 vaccine was more likely to cause Sweet syndrome than subsequent doses. Sweet syndrome may occur after COVID-19 vaccination. Clinicians should consider Sweet syndrome in addition to common adverse reactions such as anaphylaxis and infection when a patient presents with acute fever accompanied by nodular erythema, pustules, and edematous plaques after COVID-19 vaccination.

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Introduction

Since the outbreak of COVID-19 pneumonia in 2020, the cumulative number of global infections has risen sharply. Given its rapid spread and the constant emergence of variants, governments and vaccine regulatory systems around the world have invested significant resources to support the rapid development and licensing of COVID-19 vaccines since the start of the pandemic.[1]

Vaccine types include but are not limited to protein subunit (PS), viral vector (nonreplicating), DNA, inactivated virus (IV), RNA, viral vector (replicating) (VVr), and viral vector (replicating) (VVR).[2]

However, while vaccines protect people's health, there are still some adverse reactions.[3] Adverse reactions caused by vaccines can be roughly divided into systemic symptoms (fever, weakness, lethargy, etc.) and local symptoms (skin swelling, erythema, papules, etc.). Although the incidence of Sweet syndrome is not high in the population after vaccination, it should be given more attention because it is generally associated with hematological malignancies clinically.[4,5]

rAcute febrile neutrophilic dermatosis, now also known as Sweet syndrome (SS), was first described by Robert Douglas Sweet.[6] It is a form of neutrophilic dermatosis, an inflammatory skin condition characterized histopathologically by neutrophil infiltration while there is no evidence of infection.[7]

The purpose of this paper was to summarize the similar characteristics between different patients by giving examples of SS patients after the COVID-19 vaccine and to review previous relevant studies to provide possible directions for future research on the pathogenesis of Sweet Syndrome.

Methods

Search strategy

We searched the databases from inception to January 8, 2023, including the PubMed and Embase databases. The search methods used a combination of subject and free words, including Sweet syndrome, acute febrile neutrophil dermatosis, dermatosis, SAS-CoV-2, COVID-19, and vaccine (Figure 1).

Data extraction

We used a self-designed table to extract relevant information of the patients, including country, sex, age, type of vaccination, number of vaccinations, underlying diseases, duration of onset

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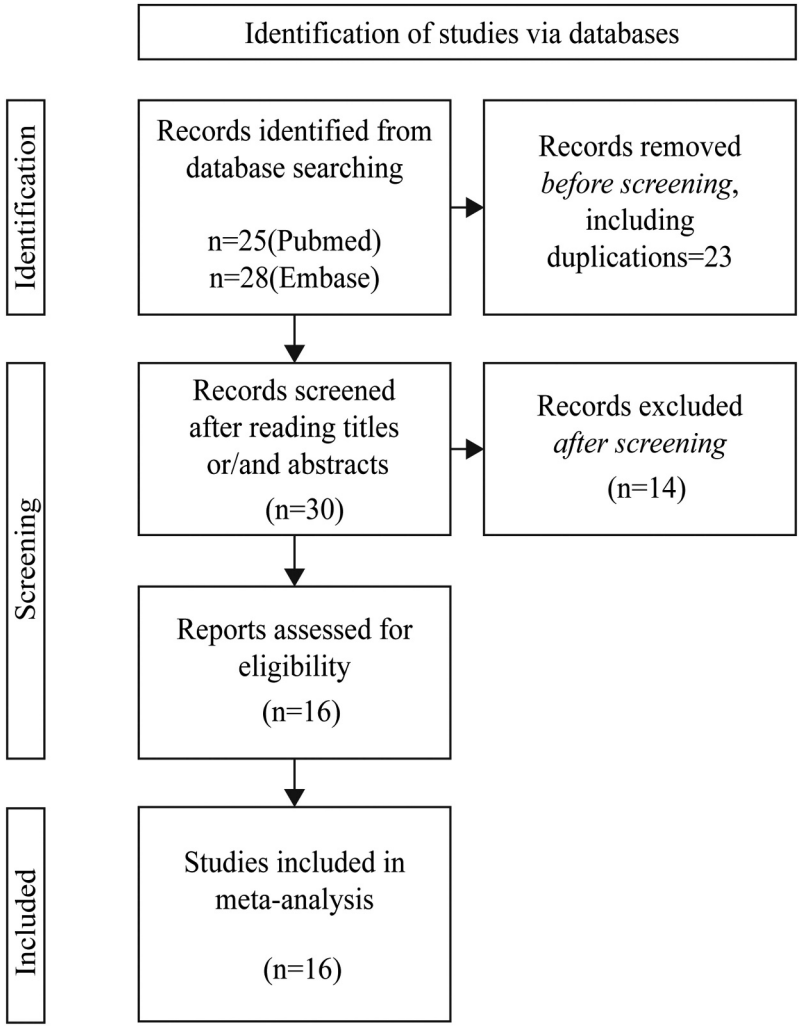

Figure 1. PRISMA flow diagram for study selection.

after vaccination, clinical manifestations, laboratory tests, treatment plan, course of disease and prognosis.

Results

Basic information

We initially identified 53 studies. A total of 23 articles were removed after an initial screening of the titles and abstracts. Among the other 30 studies, 16 articles were included through full-text screening. The patient information is summarized in Table 1. Sixteen patients (8 females, 7 males, 1 unknown) were mainly from Europe (8 in total, including 4 in Italy, 2 in France, 1 in Croatia, and 1 in Poland), with a median age of 60 years (36–87 years). All patients were vaccinated with the COVID-19 vaccine, including six with the Pfizer/BioNTech BNT162b2 mRNA vaccine, five with the Oxford-Astra Zeneca AZD1222 vaccine, and two with Johnson & Johnson Ad26.COV2. vaccine. Two patients received the mRNA-1273 vaccine from Moderna, and one patient received the inactivated vaccine from Sinovac Life Sciences. When clinical symptoms occurred, 16 patients completed the first dose of vaccine, 1 patient completed the second dose of vaccine, 1 patient received the second dose of vaccine after treatment, and 1 patient completed the third dose of vaccine after treatment and monitoring. Seven patients had a history of underlying diseases, mainly hypertension and diabetes.

Clinical manifestations

The clinical characteristics of the 16 patients included are summarized in Table 2. From 8 hours to 1 month from vaccination to the onset of clinical symptoms, all patients had skin reactions such as red plaques, including skin papules in 8 patients, which were mostly located on the hands and feet. Oedema occurred in 4 patients. Pain nodules were found in 4 patients. Pustules were found in 3 patients (2 on the extremities and 1 on the fingertips). In addition, one patient presented with neurological symptoms characterized by myoclonus and tendon hyperreflexes.

Laboratory examination

A summary of the laboratory test results is shown in Table 2. Of the 16 patients, 12 had elevated neutrophil levels, 9 had elevated C-reactive protein levels, 3 had elevated erythrocyte sedimentation rate (ESR), 1 had elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and 1 had

Table 1. Basic information of the 16 included patients.

Reference	Year	Region	Age	Gender	Past medical history	Vaccine type	Vaccination times	Time of onset after vaccination
Anne-Sophie Darrigade et al.[29]	2021	France	45	F	None	Pfizer-BioNTech mRNA vaccine	1	24 h
N. Ben Salah et al.[30]	2022	Tunisia	65	F	None	Sinovac Life Sciences, Beijing	2	8 h after the first dose
Marco Capassoni et al.[31]	2021	Italy	37	F	None	Oxford-AstraZeneca AZD1222 COVID-19 vaccine	1	4 days
T. Zagar et al.[32]	2021	Croatia	49	M	None	Oxford-AstraZeneca AZD1222 COVID-19 vaccine	1	10 days
Min Jae Kim et al.[33]	2022	Korea	60	M	Diabetes	Pfizer-BioNTech mRNA vaccine	1	2 weeks
Subhajit Sadhukhan1 et al.[34]	2022	India	36	M	Unknown	Oxford-AstraZeneca AZD1222 COVID-19 vaccine	1	1 months
Daichi Hoshina et al.[35]	2021	Japan	87	F	Unknown	Tozinameran BNT162b2 mRNA vaccine	1	6 days
Agata Bechtold et al.[36]	2022	Poland	44	F	Unknown	Johnson & Johnson, Janssen	1	7 days
A. Sechi et al.[37]	2021	Italy	69	F	Overweight, hypertension, Dyslipidemia, Iron-deficiency anemia	Oxford-AstraZeneca AZD1222 COVID-19 vaccine	1	12 days
Neha Kinariwalla et al.[38]	2022	USA	54	M	None	Johnson & Johnson, Janssen	1	9 days
Gabriel Torrealba-Acosta et al.[39]	2021	USA	77	M	Coronary artery disease,Hyperlipidaemia, hypothyroidism	Moderna mRNA-1273	1	1 day
Carmen Cantisani et al.[40]	2022	Italy	81	F	Unknown	Pfizer-BioNTech mRNA vaccine	2	2 weeks after the second dose
Sarra Ben Rejeb et al.[41]	2021	Tunisia	68	Unknown	Hypertension, Type 2 diabetes	Pfizer-BioNTech mRNA vaccine	Unknown	24 h
Frederic Pelchat et al.[42]	2022	Canada	60	M	A monoclonal gammopathy Sweet syndrome following upper respiratory tract infection	Moderna mRNA-1273	3	2 days after the first dose
Maria Efenesia Baffa et al.[43]	2021	Italy	52	M	Postoperative chemotherapy for retroperitoneal liposarcoma	Pfizer-BioNTech mRNA vaccine	1	72 h
Imran Majid et al.[44]	2021	India	65	F	Hypertension	Oxford-AstraZeneca AZD1222 COVID-19 vaccine	1	7 days

[†]F, female; [‡]M, male;, [§]USA, United States of America.

abnormal monoclonal IgA λ-positive based on serum protein electrophoresis.

Pathological examination

A summary of the pathological examination results is shown in Table 2. The main manifestations of skin biopsy were dermal neutrophilic infiltration (13 patients), dermal papillary edema (7 patients), and vascular interstitial and vascular wall neutrophilic infiltration (5 patients). A bone marrow biopsy in 1 patient indicated myelodysplastic syndrome (MDS).

Treatment

The treatment and prognosis of the 16 patients included are summarized in Table 2. Drug therapy included systemic corticosteroid therapy alone (9 patients), local corticosteroid therapy alone (2 patients), corticosteroid combined with clarithromycin and valaciclovir (1 patient), corticosteroid combined with cyclosporine (1 patient), corticosteroid combined with indomethacin (1 patient), corticosteroid combined with antibiotic therapy (1 patient), corticosteroid combined with colchicine (1 patient), and corticosteroid combined with doxycycline, tramadol and ichthyolipid (1 patient). One patient received hyperbaric oxygen therapy.

Eleven patients recovered, one patient remained under treatment, and four patients had an unknown outcome. In the patients who have been cured, the course of disease varied from five days to four months.

Data analysis

To explore the relationship between the incidence of Sweet syndrome and vaccine types, we reorganized the table (Table 3). Sweet syndrome due to COVID-19 vaccines is a rare complication with a low incidence and a low reported number. Therefore, the characteristics of data presentation need to be supplemented and improved after more patients are added. We propose several possibilities based on the available data. The patients were mainly middle-aged and elderly. We found that regardless of the vaccine type, the first dose was more likely to cause Sweet syndrome than subsequent doses.

Table 2. Patients from respective case reports included in the analysis.

Reference	Age	Gender	Clinical presentation	White blood cell count; any other laboratory examination	Histopathological analysis	Treatment	Course of disease	Outcome
Anne-Sophie Darrigade et al.[29]	45	F	Erythematous infiltrated papulosis located all over the body, without face involvement	Neutrophils count (8.77 G/L)	Dermal papillary edema.;dense infiltration around vessels, appendages and interstitium in the superficial and deep layers of skin	Systemic steroid therapy for five days	5 days	Recovery
N. Ben Salah et al.[30]	65	F	Fever, oval tenderness plaque with clear boundary on hands and feet. Bilateral purple edema plaques at metacarpophalangeal joint, distal and proximal interphalangeal joint and palm	Neutrophilia (86% of total leucocyte count equal 9560/mm^3,CRP of 42.3 mg/L,ESR of 60 mm/h	Papillary dermal evident edema with diffuse neutrophil dermal infiltration.	High potency topical steroids for 15 days	10 days	Recovery
Marco Capassoni et al.[31]	37	F	Rash,arthritis of metacarpophalangeal joints, pitting edema of hands and feet, muscle weakness, foot neuropathic pain.	13.3×10^9/L leukocytes with 76.3% of neutrophils	Neutrophilic pustular dermatitis at different evolutive states sometimes with the presence of necrotizing neutrophilic infiltrate with nuclear debris ("nuclear dust")	Empirical course of clarithromycin and valaciclovir before steroid infusion and for the following two weeks.	7 days	Recovery
T. Zagar et al.[32]	49	M	Erythematous papules and targetoid plaques, along with haemorrhagic blisters on the hands and feet.	Unknown	Massive oedema of the papillary dermis, diffuse neutrophil infiltration	Systemic corticosteroids, thromboprophylaxis and hyperbaric oxygen therapy	Unknown	Unknown
Min Jae Kim et al.[33]	60	M	Painful erythematous nodular eruption on the face, trunk, and limbs	leukocyte count of 3.57×10^3/μL with 80.1% neutrophils, platelet count of 44×10^3/μL; CRP level of 12.56 mg/dl, ESR of 27 mm/h	Papillary dermal edema, multinucleated giant cells, and prominent neutrophilic infiltration; bone marrow biopsy showed MDS	Cyclosporine (200 mg/day) and prednisolone (20 mg/day)	2 weeks	Recovery
Subhajit Sadhukhan1 et al.[34]	36	M	Multiple suppurative lesions at fingertips, multiple painful nodules in both legs, multiple tender deep pustules in wrist and ankle joints, erythema around the lesions, and edema in the pulp of both thumbs and left index fingers	ESR (62 mm/1st hour)	Predominantly peri- appendageal lymphomononuclear inflammatory infiltrate in the deeper dermis.	Dapsone 100 mg once daily and Indomethacin.	4 months	Recovery
Daichi Hoshina et al.[35]	87	F	Erythema and papule on the right leg, edema aggravating, forming bullae, and later edematous erythema extending to the thigh, forming purpura and massive hemorrhagic bullae	20 000/μ L of white blood cells (91.1% of neutrophils), 14 U/L of AST, 7 U/L of ALT, 11 U/L of CPK, and 22 mg/dL of CRP.	Obvious edema in dermal papillary layer, inflammatory infiltration in dermis, mainly composed of mature neutrophils	i.v. cefazoline 3 g/day and oral prednisolone 0.5 mg/kg/day	Unknown	Additional 8 weeks was required for complete recovery.
Agata Bechtold et al.[36]	44	F	Tender purulent vesicles and well demarcated edematous plaques consisting of papules and vesicles on the limbs. erosions on the sides of the tongue and in the vestibulethe tongue covered with yellowish coating	CRP level was 92 mg/dl, white blood cell count was 9.72×103/μl with neutrophilia 87.1%.	Unknown	oral prednisone 0.6 mg/kg/day and intravenous doxycycline 200 mg/day; s.c. tramadol 200 mg/day and 3% ichthyol solution	2.5 months	Recovery
A. Sechi et al.[37]	69	F	Evolutive polymorphism of early annular lesions evolving into large, thickened ulcerated plaques	Unknown	Mildly acanthotic epidermis with subepidermal oedema and intense interstitial neutrophilic infiltrate in the dermal layer.	Steroid administration (prednisone 1 mg/kg/day for 4 weeks, then slow tapering)	Unknown	Recovery

(*Continued*)

Table 2. (Continued).

Reference	Age	Gender	Clinical presentation	White blood cell count; any other laboratory examination	Histopathological analysis	Treatment	Course of disease	Outcome
Neha Kinariwalla et al.[38]	54	M	Erythematous, fissured tongue,flesh-colored and erythematous plaques on the scrotum, erythematous and targetoid macules on the plantar	Leukocytosis (10.84 × 103/ uL) with 90% neutrophils, 29 mL/h of ESR, and 19.6 mg/L of CRP. Positive abnormal monoclonal IgA lambda.	A dense interstitial and perivascular neutrophilic infiltration with leukocytoclasia and focal fibrin deposition in blood vessel walls.	10-day course of steroid	10 days	Recovery
Gabriel Torrealba-Acosta et al.[39]	77	M	Scattered dark red, non-scale, edematous papular plaques and scattered non-follicular pustules.Intermittent and irregular orofacial movement and bilateral upper limb myoclonus.Deep tendon hyperreflexia	120×10^6/L leucocytes (77% lymphocytes).Elevations in CRP,CPK,ferritin.	Intracorneal microabscesses, oedematous papillary dermis, a band-like infiltrate of predominantly neutrophils and histiocytoid cells with nuclear debris in the superficial dermis	4-day course of 1 g methylprednisolone once a day	4 days	Recovery
Carmen Cantisani et al.[40]	81	F	Erythematous plaques on the trunk, back and abdomen	Neutrophil count (>6000 cells/μL) and elevated CRP	A dense neutrophilic infiltrate	Systemic steroid therapy	Unknown	Recovery
Sarra Ben Rejeb et al.[41]	68	Unknown	Painful erythema or erythema on the palm, purple nodules and nodules	Neutrophilia with 68.7% neutrophils	The infiltration of neutrophils dominates the superficial and middle dermis and extends around the blood vessels.	High-dose local corticosteroid treatment.	10 days	Recovery
Frederic Pelchat et al.[42]	60	M	Multiple, tender, indurated erythematous papules and plaques over his face, trunk, upper, and lower limbs.Mild malaise and fatigue	Neutrophilia at 8310×10^9/L, elevated ESR at 15 mm/h.	Superficial and middermal histiocytoid cells infiltration with a few accompanying T lymphocytes	Systemic steroid therapy	Unknown	Recovery
Maria Efenesia Baffa et al.[43]	52	M	Scattered plaques which show overwhelming vesicles and pustules, or target-like appearance due to a central hemorrhagic crust	Unknown	A dense and diffuse mixed inflammatory infiltration with a predominance of neutrophils, with subtle perivascular nuclear dust, dilatated capillaries, and prominent edema of the upper dermis	Methylprednisolone intravenously	3 weeks	Recovery
Imran Majid et al.[44]	65	F	Dark red, symmetrical, unclear boundary, rising surface temperature, tender-touched plaques	leukocytosis (14,000/mm^3, 82% of total leukocyte count),ESR(60 mm in 1 h), highly positive CRP.	The dense neutrophilic infiltrate in dermis,the dermal edema present	Injectable dexamethosone Oral colchicine topical corticosteroids	1 week and is still on treatment	Still on treatment

[†]ALT,alanine aminotransferase; [‡]AST,aspartate aminotransferase; [§]CPK,phosphocreatine kinase; [¶]CRP,C-reactive protein; [††]ESR,erythrocyte sedimentation rate; [‡‡]F,female; [§§]i.v.,intravenous injection; [¶¶]M,male; [†††]MDS,myelodysplastic syndrome; [‡‡‡]s.c.subcutaneous injection.

Table 3. Sweet syndrome cases information classified by vaccine type.

Type	References	Gender	Age	Past History	Dose of vaccine when clinical symptoms occurred	Onset time	Neutrophil Count
Johnson& Johnson, Janssen Ad26. COV2.S SARS-CoV-2 vaccination	Agata Bechtold et al.[36]	F	44	Unknown	1	7 days	9.72 × 10^9/L
	Neha Kinariwalla et al.[38]	M	54	None	1	9 days	10.84 × 10^9/L
Moderna vaccine mRNA-1273 vaccine	Gabriel Torrealba-Acosta et al.[39]	M	77	Coronary artery disease, Hyperlipidaemia Hypothyroidism	1	1 days	15.5 × 10^9/L
	Frederic Pelchat et al.[42]	M	60	History of burns Sweet Syndrome	1	2 days	8.31 × 10^9/L
Oxford-AstraZeneca AZD1222 vaccine	Marco Capassoni et al.[31]	F	37	None	1	4 days	13.3 × 10^9/L
	T. Zagar et al.[32]	M	49	None	1	10 days	Unknown
	Subhajit Sadhukhan1 et al.[34]	M	36	Unknown	1	1 month	Unknown
	A. Sechi et al.[37]	F	69	Overweight, Hypertension, Dyslipidaemia, Irondeficiency anemia	1	12 days	Unknown
	Imran Majid et al.[44]	F	65	Hypertension	1	7 days	14 × 10^9/L
Pfizer/BioNTech BNT162b2mRNA vaccine	Anne-Sophie Darrigade et al.[29]	F	45	None	1	24 hours	8.77 × 10^9/L
	Min Jae Kim et al.[33]	M	60	Diabetes	1	2 weeks	3.57 × 10^9/L
	Carmen Cantisani et al.[40]	F	81	Unknown	2	2 weeks	Unknown(>6 × 10^9/L)
	Sarra Ben Rejeb et al.[41]	unknown	68	Hypertension, Diabetes Mellitus	unknown	24 hours	Unknown
	Maria Efenesia Baffa et al.[43]	M	52	Retroperitoneal liposarcoma	1	72 hours	Unknown
Sinovac Life Sciences vaccine	N. Ben Salah et al.[30]	F	65	None	1	8 hours	9.56 × 10^9/L
Tozinameran	Daichi Hoshina et al.[35]	F	87	Unknown	1	6 days	11.5 × 10^9/L

F, Female; M, Male.

Discussion

In summary, we have summarized a series of cases of vaccine-induced Sweet syndrome. We recognize that this is a rare adverse event caused by a vaccine and needs to be distinguished from other adverse events. Although the incidence of Sweet syndrome is not high in the population after vaccination, it should be given more attention because it is generally associated with hematological malignancies clinically.[4,5] Previous retrospective studies have suggested that the onset of SS may be associated with some malignant tumors.[8–10]

A classification of SS is based on its clinical background, including classical SS, cancer-associated SS, and drug-induced SS. According to the classification of von den Driesch et al., it is classified as idiopathic, inflammatory (associated with infection or inflammatory disease), neoplastic (associated with cancer or other paraneoplastic conditions) and pregnancy associated. The vaccine-induced SS discussed in this paper is generally classified as inflammatory.

Because the symptoms and signs of SS are very similar to those of many diseases, especially infectious diseases, the diagnostic method of exclusion is usually used in the diagnosis of SS (Table 4), and it is to be differentiated from other infectious diseases (local bacterial and fungal infections, etc.), inflammatory diseases (erythema nodosum, vasculitis, cutaneous sarcoidosis, etc.), and skin manifestations of malignant tumors. The diagnostic criteria for SS consist of two major symptoms and four minor symptoms. SS is diagnosed when all major symptoms and at least three minor symptoms are met.[7]

Table 4. Modified diagnostic criteria for Sweet's syndrome.[6]

Major criteria
(1) Abrupt onset of tender or painful erythematous plaques or nodules, occasionally with vesicles, pustules, or blisters.
(2) Predominantly neutrophilic dermal infiltrate without leukocytoclastic vasculitis.

Minor criteria
(1) Preceded by a nonspecific respiratory or gastrointestinal tract infection or vaccination or associated with:
- Inflammatory diseases such as chronic autoimmune disorders, infections
- Hemoproliferative disorders or solid malignant tumors
- Pregnancy

(2) Fever >38°C
(3) Abnormal laboratory values at presentation (three of four):
- Erythrocyte sedimentation rate >20 mm/h
- Elevated C-reactive protein levels
- Leukocytosis > 8,000
- Neutrophilia > 70%

(4) Excellent response to treatment with systemic corticosteroids or potassium iodide

Both major and two minor criteria are needed for diagnosis.

In regard to clinical manifestations, there is no difference between classic SS and vaccine-induced SS. The Naranjo score is one of the reasons that is considered to be caused by vaccines.

At present, systemic glucocorticoids are the preferred treatment for SS and have the characteristics of quick action and obvious effects. In addition, potassium iodide, colchicine, and Tripterygium wilfordii preparations can also obtain better results; dapsone, doxycycline and cyclosporine are also effective, but attention should be given to the occurrence of adverse reactions during treatment.

We can speculate on the correlation between vaccines and Sweet syndrome because Sweet syndrome has also been caused

by other vaccines, not only COVID-19 vaccines. Second, according to the results of laboratory tests, it is not difficult to infer that the patient's immune function is abnormal, which is manifested as an increase in the number of white blood cells, an increase in erythrocyte sedimentation rate, and an increase in various inflammatory factors.

However, this is different from the common immune-related side effects caused by vaccines.

The clinical characteristics of SS patients were fever, leucocytosis, and tender red papules and patches on the skin, and histopathology showed infiltration of neutrophils and neutrophil fragments in the dermis.

It is important to note that common skin reactions caused by vaccines differ markedly in clinical presentation. Injection site reactions are manifested as skin reactions around the injection site, local edema, erythema, and hard lumps with pain sensation.[11] The neck and chest limbs may have various types of eruptions: erythematous confluent, maculopapular, papulovesicular, etc.[12]

Vaccine-induced hypersensitivity reactions can also be distinguished from SS. Vaccine-induced hypersensitivity reactions should first be characterized by the presence or absence of the allergen (usually vaccine excipients). The general clinical manifestations of patients are dyspnea, chill, chest pain, tachycardia, hypertension, anaphylaxis, etc.[13]

We believe that the appearance of inflammatory factors may influence the development of the disease. Early reports reported that Ig-A inhibition affected the chemotaxis of multinucleated leukocytes in neutrophilic skin diseases, which corresponded to the positive abnormality of monoclonal IgA-λ in serum protein electrophoresis in the included patients.[14] In addition, the increase in many inflammatory factors in this patient may suggest that the vaccine as a stressor activates immune cells to produce immune-related cytokines and then affects the chemotactic process of neutrophils.

In addition, the neutrophilia and findings on bone marrow biopsy suggest that the vaccine may have affected the differentiation of myeloid precursor cells.

The pathophysiological mechanism of vaccine-induced SS is still not unified at present. SS was initially thought to be a hypersensitivity phenomenon, which was supported by frequent occurrence after infection and less involvement of the remaining organs in response to glucocorticoid therapy. Another theory tries to explain the characteristics of fever and increased erythrocyte sedimentation rate in SS from the perspective of cytokine involvement. Previous studies have shown that elevated G-CSF is also a common feature in many patients with SS.[15] G-CSF, also known as granulocyte colony stimulating factor, stimulates the survival, proliferation, differentiation, and functioning of precursor and mature neutrophils. As a clinical drug, it can reduce myelosuppression caused by chemotherapy and avoid severe neutropenia. However, some previous patients have reported that G-CSF treatment has resulted in Sweet syndrome in patients[16–19] (Figure 2). This phenomenon makes people consider the relationship between G-CSF and SS.

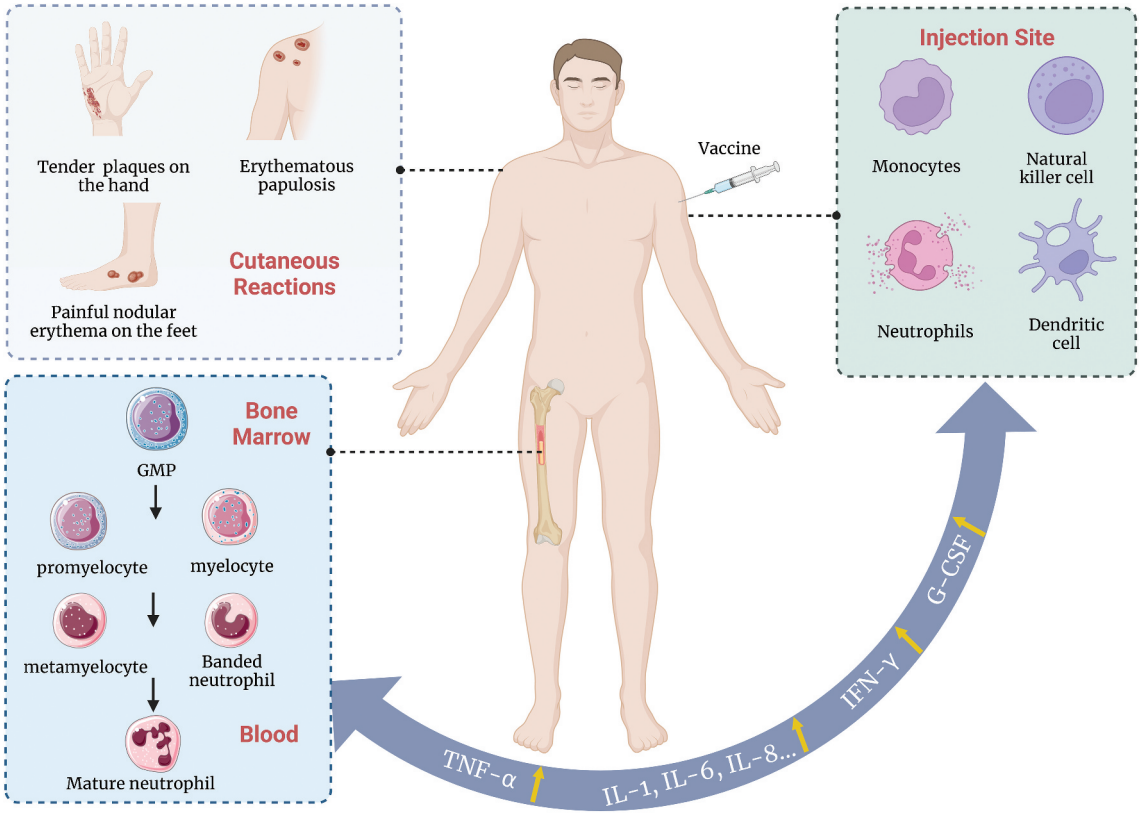

Figure 2. Vaccine-introduced Sweet syndrome. When the vaccine enters the human body as a stimulus, it activates human immune cells to respond and affects the innate immune memory, which in turn temporarily affects the differentiation and migration process of neutrophils, which is manifested as changes in the content of interleukins, G-CSF and other cytokines, and then causes Sweet syndrome and produces external cutaneous reactions. GMP: Granulocyte- Macrophage Progenitors. Image created with BioRender.com, with permission.

In recent years, studies on the memory mechanism of innate immunity have completed our understanding of human immune function.[20] We know that the specificity of adaptive immune memory is ensured by the recombination, cloning and expansion of immunoglobulin family genes. However, the basic mechanism of nonspecific enhancement of innate immune cells depends on epigenetic, transcriptional, and metabolic programs after transient stimulation. These procedural changes lead to enhanced responses to secondary exposure to various stimuli. On the one hand, trained immunity enhances the human body's response to infection and vaccines and enhances the innate immune response. On the other hand, this stronger immunity may contribute to the development of cardiovascular diseases, autoimmune diseases and neurodegenerative diseases.

It is not clear why neutrophilic dermatoses can occur with pneumococcal, influenza and BCG vaccines (Bacillus Calmette – Guerin vaccine), not just COVID-19 vaccines.[21–23] Recent studies on innate immune memory will help us to complete our knowledge of the human immune system and obtain an answer to this question. When injected into the human body, vaccines stimulate not only adaptive immunity but also innate immunity. This stimulation first appears as an acute local response involving different local innate immune cell subsets, such as neutrophils, macrophages, or dendritic cells, and when strong enough, stimulates a central response in the individual's bone marrow.[24] It induces long-term metabolic and epigenetic reprogramming of hematopoietic stem cells, which are transmitted to their daughter cells and promote the establishment of long-term innate immune memory responses[25,26] (Figure 2). The intensity of this innate immunity is influenced not only by exogenous stimuli but also by endogenous factors such as hyperglycemia[27] and catecholamines.[28] This may be one of the reasons for the low incidence rate of sweet syndrome caused by the vaccine.

Limitations

Our research still has several limitations. First, the patient data in the table came from the articles in the selected database, and some reports with incomplete data were excluded, which may affect the report. Second, the incidence of vaccine-induced Sweet syndrome is low, and the number of patients is small. A larger number of patients is still needed to provide reliable clinical data for research. Third, there is no direct experiment to verify the hypothesis in this paper, and it should be verified by other experimental designs in the future.

Conclusions

Clinicians should be aware of Sweet syndrome in addition to common adverse reactions such as anaphylaxis and infection when a patient presents with acute fever accompanied by nodular erythema, pustules, and edematous plaques after COVID-19 vaccination. Early diagnosis and accurate management are necessary for Sweet syndrome because the current first-line treatment can significantly improve the skin symptoms of Sweet syndrome.

Abbreviations

PS:	Protein Subunit
DNA:	Deoxyribonucleic Acid
IV:	Inactivated Virus
RNA:	Ribonucleic Acid
VVr:	Viral Vector (replicating)
VVR:	Viral Vector(Replicating)
SS:	Sweet Syndrome
G-CSF:	Granulocyte Colony-Stimulating Factor
BCG vaccine:	Bacillus Calmette – Guerin vaccine

Authors' contributions

JYL and FBY contributed equally as first authors. ZMY contributed as correspondence author. ZMY conceived and designed the study; JYL and FBY carried out the literature searches, extracted the data; DLP contributes to polishing articles; ZMY, JYL, FBY and DLP revised the manuscript. All authors read and approved the final manuscript.

Disclosure statement

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its additional information files.

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